EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application: Jacques PARIS et al.
Serial No 09/423,109
Filed on: October 29, 1999

Art Unit: 1616
Examiner: Qazi

For: New hormonal composition and its use.

DECLARATION UNDER 37 C.F.R. § 1.132

Honorable Commissioner of Patents and Trademarks
Washington, DC 20231

Sir:

The undersigned, Jean-Louis THOMAS, of France, declares as follows:

1. I am a Medical Doctor (MD) and a Pharmacist holding such degree from the University of Nancy (France).

I have fulfilled the following functions:

1969-1972:	Pharmacist Resident, Nancy hospitals
1973-1975:	Consulting Pharmacist, Nancy hospitals
1975-1976:	Medical Resident, Hôpital des Armées, Nancy
1976-1980:	Medical Resident, Nancy hospitals
1980-1984:	Assistant Resident, Centre Hospitalier Universitaire (CHU), Nancy
1984-1985:	Senior Consultant-Assistant professor, CHU, Nancy
1985-1987:	Senior Consultant, Nancy hospitals
Since 1985:	Director of the clinical Research and Development Department, Théramex Laboratory, Paris
Since 1988:	Senior Consultant, Paris hospitals (Department of Endocrinology, Diabetology and Nutrition, CHU Henri-Mondor, Créteil)

I devoted many years of my professional life in the field of Endocrinology and Clinical Pharmacology.

I am the applicant of several publications, many of them on the use of hormones in women.

I direct a team that develops hormones for use in contraception and menopause.

2. I am a co-inventor of the captioned application.

3. I have read the prior art documents cited against the present application and I am of the opinion that they do not suggest the claimed method of treating estrogenic deficiencies in women.

4. I present hereafter the arguments which sustain my opinion.

4.1. PLUNKETT (US Re 36,247) fails to disclose Nomegestrol acetate as progestin and the properties thereof.

Plunkett disclosed a method for treatment of menopausal disorders comprising continuous or intermittent administration of an estrogen / progestin combination, claiming that all estrogens and all progestins can be used indiscriminately, providing that equivalent doses are administered. Nevertheless, the Applicant has the opinion that the Plunkett's patent cannot be opposed to the present application because they did not claim the use of NOMAC and because the choice of active doses cannot be based on a rule of "equivalence". Anybody skilled in the art knows that each progestin has its own pharmacological profile and cannot automatically be replaced by any other available progestin and that the rule of equivalence is not in accordance with scientific knowledge.

- *NOMAC brings original properties*

  NOMAC is not comparable to other progestins; it has an original pharmacological profile which is not shared with any other available progestin. In summary, contrary to 19 nor-testosterone derivates, it does not bring any androgenic and estrogenic residual activity and, contrary to 17α-hydroxyprogesterone derivatives, it has a strong antigonadotropic activity (Table 1).

Table 1: **NOMAC pharmacological profile**

NOMAC	OTHER PROGESTINS	
	progesterone derivatives	19-nor testosterone derivatives
Strong progestagen activity	Strong progestagen activity, except progesterone	
without androgenic residual effects without estrogenic residual effects without gluco-corticoid residual effects without deleterious metabolic effects	with or without androgenic residual effects without estrogenic residual effects with or without gluco-corticoid residual effects with or without deleterious metabolic effects	with androgenic residual effects with estrogenic residual effects with gluco-corticoid residual effects with deleterious metabolic effects
Strong antigonadotropic activity	Slight antigonadotropic activity	Strong antigonadotropic activity

- *The "equivalence" rule has no scientific support*

The choice of active doses cannot be based on the "equivalence" rule for different reasons:

1. as described above, the profile of progestins is very different in term of pharmacological activity and adverse effects so that one progestin cannot automatically replace another for a given therapeutic use;

2. active doses must be chosen case by case from clinical data and/or opinion of anybody skilled in the art because:

   a. there is no agreement about active doses of a given progestin; minimum dose and maximal doses are very different between patents claiming the same therapeutic use; an example is given in Table 2: considering WO 95/1/17194, EP 025607 A1 and Plunkett's patent, minimal and maximal active doses of levonorgestrel, desogestrel and 3-ketodesogestrel are very different.

Table 2: Differences in active doses (µg/day) in different patents claming for the same therapeutic use

Progestin	Patent	Dose (µg/day)	
		Mini	Maxi
levonorgestrel	WO 95/17194	60	125
	EP 025607 A1	25	100
	PLUNKETT	25	75
gestodene	WO 95/17194	50	75
	EP 025607 A1	10	70
desogestrel	WO 95/17194	60	150
	EP 025607 A1	25	100
3-ketodesogestrel	WO 95/17194	60	150
	EP 025607 A1	25	100
norethisterone	WO 95/17194	350	750
	EP 025607 A1	85	350
	PLUNKETT	150	1000

   b. active doses of progestins are depending on pharmacological and/or clinical targets; consequently, it is impossible to propose equivalent doses without indicating the target. Considering HRT, two targets can be chosen, either histological effects on the endometrium or effects on menstruation. Data presented in Table 3 clearly show that doses claimed in the Plunkett's patent are very different from values reported in papers from Neumann and Kuhl: for these two well-known specialists of progestins, active doses of levonorgestrel, norgestrel, norethisterone, norethisterone acetate, norethynodrel and lynestrenol on endometrium and menstruation are much higher than doses claimed by Plunkett using his equivalence rule (Table 3).

Table 3: **Published active doses of progestins depending on clinical efficacy targets**

Progestin	Plunkett's patent		Neumann's paper		Kuhl's paper
	Mini	Maxi	Endometrium transformation	Withdrawal bleeding delay	Endometrium transformation
levonorgestrel	25	75			400
norgestrel	50	150	1200	2000	
norethisterone	150	1000	12500	5000	10000
norethisterone acetate	100	1000	4500		
medroxyprogesterone acetat	1000	15000	5500	25000	
norethynodrel	200	5000	10000	7500	
allylestrenol	1000	10000	1750		
lynestrenol	100	2000	5000		
cyproterone acetate	100	10000	1000		2000

In grey, progestins for which active dose calculated using the equivalence principle are much lower that active doses published by Neumann and Kuhl

In conclusion, the range of active doses of each progestin must be chosen case by case from clinical data and/or the expertise of anybody skilled in the art and cannot derive from a standard equivalence ratio as proposed by Plunkett.

- *Progestins continuously given with an estrogen induce an endometrial atrophy.*

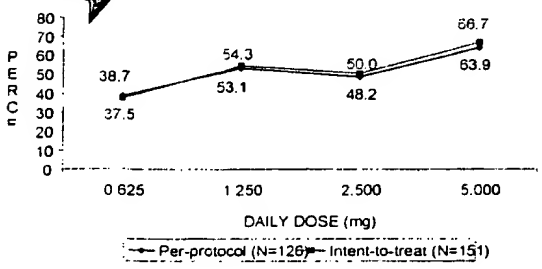
After the issue of the Plunkett's patent, Nomegestrol acetate was shown to have a different effect on endometrium (Fig 1); this effect is characterized by a dissociation between anti-estrogenic and progestagen activity: at low doses, the anti-estrogenic effect is predominant and endometrium is atrophic; at high doses, the progestagen effect is predominant and the endometrium is secretory. Unexpectedly, even with high nomegestrol acetate doses, a large majority of women are amenohrreic (Fig 1). This is a characteristic of nomegestrol acetate, never described for other progestins, which can bring clinical advantages, especially in term of acceptability of treatment and consequently compliance, due to an increase of the percentage of no-bleeding pattern.

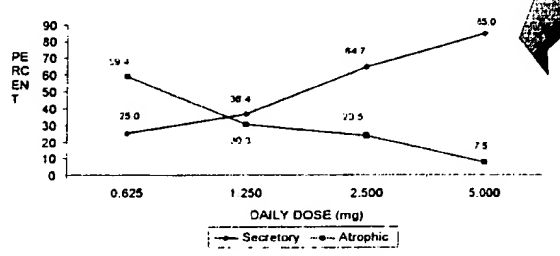
Figure 1 : Endometrial effects of E2/nomegestrol acetate continuous combination

Clinical examples

151 postmenopausal women (treated for 6 months)

Dose E2V mg - NOMAC mg	2.0 0.625	2.0 1.25	2.0 2.5	2.0 5.0
Number of patients	37	37	38	38
Amenorrhea (%)	38.7	54.3	50.0	66.7
Secretory endometrium (%)	25.0	36.4	64.7	85.0
Atrophic endometrium (%)	59.4	30.3	23.5	7.5





4.2. The Blanc et al. reference discloses continuous hormone replacement therapy for menopause combining oral 2.5 mg/day nomegestrol acetate and either percutaneous 17β-estradiol gel (1.5 mg/day), transdermal 17β-estradiol patch (50 µg/day) or oral estradiol valerate (2 mg/day).

According to the results discussed on pages 905-906, the amenorrhea rate (or cycles with no bleeding) was 60 % when oral nomegestrol acetate was combined with oral estradiol valerate, as compared to 78 % when oral nomegestrol acetate was combined with percutaneous estradiol.

There is no suggestion whatever in Blanc et al. to lower the dose of nomegestrol acetate with a view towards correcting estrogen deficiencies or preventing osteoporosis, and then, one of ordinary skill in the art would select neither the regimen when both the nomegestrol and the estrogen are administered orally, nor the range of doses proposed in this present application.

In fact, Blanc et al. teaches that the rate of amenorrhea achieved with continuous combined HRT for menopause is an important factor in patient compliance (page 909, left column, emphasis added).

Since according to Blanc the rate of amenorrhea is higher when nomegestrol acetate is combined with percutaneous estradiol (as discussed above), those skilled in the art seeking to improve the rate of amenorrhea and hence patient compliance would have been deterred from using an oral estrogen in combination with oral nomegestrol acetate.

Moreover, Table 2 on page 24 of the specification of the present application shows the results of biopsies of the endometrium of women treated with the combination of the invention. A comparison is made between the combination containing 2.5 mg of nomegestrol acetate (i.e. the dose disclosed in Blanc et al.) and combinations containing lower doses of nomegestrol acetate as presently claimed.

It can be seen that the number of atrophic endometria significantly increased at the doses of 1.25 mg (a 25 % increase) and 0.625 mg (a 138 % increase) of nomegestrol acetate, as compared to the dose of 2.5 mg taught by Blanc et al.

This means that the endometrium is protected because when an endometrium is atrophic then no hyperplasia (excessive growth of tissue) occurs.

At the same time, the low doses of nomegestrol acetate are insufficient to induce a secretory transformation of the endometrium (as can be seen from table 2, the number of secretory endometrium significantly decreases with the dose).

Accordingly, it is thus surprising and unexpected that at doses which are insufficient to induce a secretory transformation of the endometrium, nomegestrol acetate, when administered with an estrogen, nevertheless exerts a protecting effect on the endometrium by keeping it in atrophic state.

Such results certainly cannot be deducted from the teachings of Plunkett et al. which does not disclose nomegestrol acetate at all, or Blanc et al. which uses higher dose of nomegetrol acetate.

The skilled man would not have been motivated to use a progestin and an estrogen continuously as taught by Plunkett and to use nomegestrol acetate as progestin because Blanc et al. does not provide any incentive to do so. In addition, the effects of nomegestrol acetate on the endometrium are surprising and unexpected when taken in the light of the cited prior art.

5. Furthermore, the following examples carried out under my supervision confirm that the hormonal combination of the invention is useful for correcting estrogenic deficiencies in women and in preventing osteoporosis.

Example 1

In a double-blind multicenter placebo-controlled study, the effect of two estradiol (E2) /nomegestrol acetate (NOMAC) continuous combinations (0.5 mg E2/0.625 mg NOMAC and 1 mg E2/1.25 mg NOMAC) on symptoms related to estrogen deficiency were tested in 114 postmenopausal women.

The women were treated for 3 months and were evaluated at baseline, after 6 weeks and at the end of treatment.

The following table shows the total number of hot flushes recorded by the women within the 7 days before the evaluations.

Treatment	Baseline	6 weeks	3 months	p Value
E2 0.5 mg / NOMAC 0.625 mg	24.1 (36)	3.4 (38)	1.9 (35)	< 0.0001
E2 1 mg / NOMAC 1.25 mg	11.2 (38)	0.5 (40)	0.3 (37)	< 0.0001
Placebo	12.4 (39)	10.2 (36)	8.8 (36)	0.3186

(n) = number of women at each evaluation

The number of hot flushes did not change significantly in the placebo group, but significantly decreases in women treated with the E2/NOMAC combinations of the invention.

Example 2

In a double placebo-controlled study, the effect of two estradiol (E2) /nomegestrol acetate (NOMAC) continuous combinations (0.5 mg E2/0.625 mg NOMAC and 1 mg E2/1.25 mg NOMAC) on blood and urinary type 1-collagen C-telopeptides (CTX) were evaluated in postmenopausal women.

CTX is a bone resorption biological parameter which increases in women with risk of osteoporosis.

The following tables show the plasma and urinary CTX values observed at baseline, after 6 weeks and 3 months of treatment.

Plasma CTX

Treatment	Baseline	6 weeks	3 months	p Value
E2 0.5 mg / NOMAC 0.625 mg	0.5 (38)	0.4 (36)	0.3 (35)	< 0.0001
E2 1 mg / NOMAC 1.25 mg	0.5 (41)	0.3 (40)	0.3 (38)	< 0.0001
Placebo	0.5 (41)	0.5 (40)	0.6 (38)	0.2790

(n) = number of women at each evaluation

Urinary CTX/creatinine ratio

Treatment	Baseline	6 weeks	3 months	p Value
E2 0.5 mg / NOMAC 0.625 mg	285.5 (34)	180.8 (36)	184.0 (35)	< 0.0001
E2 1 mg / NOMAC 1.25 mg	281.9 (40)	155.0 (40)	141.4 (37)	< 0.0001
Placebo	312.8 (41)	319.9 (40)	325.7 (36)	0.5271

(n) = number of women at each evaluation

The CTX values were similar at baseline in the 3 treatment groups, but significantly decreased during treatment with the two E2/NOMAC combinations, while they increased in the placebo group.

These results show that the E2/NOMAC combinations of the invention were able to decrease bone resorption and then to prevent osteoporosis.

* * *

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 26th day of January 2006

Jean-Louis THOMAS